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ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,363	ZENG, XIAN-MING	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending. Applicant has amended claims 1, 3-5, 7-9, 11, and 13-14. Claims 16-19 are new. Receipt and consideration of Applicant's amended claims, new IDS, and remarks/arguments, submitted on May 18, 2007 are acknowledged. Applicant's amendments have necessitated new grounds of rejection (e.g. under 35 U.S.C. §103(a)).

Specification

The objection of claim 13 because of the informalities set forth in the office action mailed on November 13, 2006 **is withdrawn** per Applicant's amendments correcting the spelling of the word dihydrate.

The objection of claim 14 under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only **is withdrawn** per Applicant's amendments correcting the dependency of claim 14.

Response to Arguments

Applicant's arguments, see page 6, filed May 18, 2007, with respect to the objections of claims 13-14 as set forth in the office action mailed on November 13, 2006 have been fully considered and are persuasive. The objections of claims 13-14 have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

The rejection of claims 6-9, 12, and 14-15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained** for the reasons of record set forth on pages 2-3 of the office action mailed on November 13, 2006.

Response to Arguments

Applicant's arguments filed May 18, 2007 have been fully considered but they are not persuasive. Applicant has traversed the instant rejection by arguing that an ordinary skilled artisan would clearly understand what is meant by a pharmaceutically acceptable anti-inflammatory steroid derivative or a pharmaceutically acceptable bronchodilator as allegedly evidenced by the disclosures of USPN 5,712,263, USPN 5,434,304, and Exhibit A.

The Examiner respectfully disagrees with Applicant's traversal argument. The term steroid derivative or bronchodilator derivative is not defined in the specification, nor do the two US patents or Exhibit A define what is a derivative of a steroid or a bronchodilator. It is noted that reference to a steroid derivative in the instant application is not limited to the structure depicted in formula (I) (see abstract) of USPN 5,712,263. References to bronchodilator derivatives or formoterol derivatives in the instant application are not limited to the compounds of formula (I) as described in USPN 5,424,404. Thus, these U.S. patents do not demonstrate that terms, such as, budesonide derivative, bronchodilator derivative, or formoterol derivative have a consistent and clear art-recognized meaning. The 10th edition of the Merriam-Webster's Collegiate Dictionary (Merriam-Webster Incorporated: Springfield, Massachusetts, 1993, pp 311) defines "derivative" as, "a chemical substance related structurally to another substance and

theoretically derivable from it." For example, carbon dioxide could theoretically be derived from the combustion of a steroid or a bronchodilator. The definition of derivative in the Merriam-Webster Collegiate Dictionary does not shed light on what Applicants' intended for the meaning of a an anti-inflammatory steroid derivative or a bronchodilator derivative. Therefore, an ordinary skilled artisan would be unable to ascertain what is meant by either an anti-inflammatory steroid derivative or a bronchodilator derivative and the instant rejection remains proper.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 11 and 13-14 under 35 U.S.C. 102(b) as being anticipated by Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) **is withdrawn** per Applicant's claim amendments requiring that the claimed powder comprise carrier particulates with a VMD of from about 50 to about 250 microns and consist only of (a) a 1st particulate medicament, (b) a 2nd particulate medicament, and (c) particulate carrier as described above.

Response to Arguments

Applicant's arguments, see pages 8-9, filed May 18, 2007, with respect to rejection of claims 11 and 13-14 under 35 U.S.C. 102(b) as being anticipated by Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) have been fully considered and are persuasive. The rejection of claims 11 and 13-14 under 35

U.S.C. 102(b) as being anticipated by Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) has been withdrawn.

The rejection of claims 11-15 under 35 U.S.C. 102(b) as being anticipated by Trofast (U.S. Patent No. 6,030,604) ("Trofast") **is withdrawn** per Applicant's claim amendments requiring that the claimed powder comprise carrier particulates with a VMD of from about 50 to about 250 microns.

Response to Arguments

Applicant's arguments, see page 9, filed May 18, 2007, with respect to rejection of claims 11-15 under 35 U.S.C. 102(b) as being anticipated by Trofast (U.S. Patent No. 6,030,604) ("Trofast") have been fully considered and are persuasive. The rejection of claims 11-15 under 35 U.S.C. 102(b) as being anticipated by Trofast (U.S. Patent No. 6,030,604) ("Trofast") has been withdrawn.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 1-10 under 35 U.S.C. 103(a) as being unpatentable over Trofast (U.S. Patent No. 6,030,604) in view of Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) **is withdrawn** per Applicant's claim amendments requiring that the claimed powder comprise carrier particulates with a VMD of from about 50 to about 250 microns.

Response to Arguments

Applicant's arguments, see pages 8-9, filed May 18, 2007, with respect to rejection of claims 11 and 13-14 under 35 U.S.C. 102(b) as being anticipated by Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) have been fully considered and are persuasive. The rejection of claims 11 and 13-14 under 35 U.S.C. 102(b) as being anticipated by Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) has been withdrawn.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trofast (U.S. Patent No. 6,030,604) and Keller (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) in view of Ward et al. (U.S. Patent No. 6,616,914).

Applicant Claims

Applicant claims (1) a method of preparing a dry powder inhalation composition comprising the steps of (a) mixing a particulate carrier with a first portion of a first particulate

medicament to obtain a first mixture (b) mixing said first mixture with a second particulate medicament to obtain a second mixture, and (c) mixing said second mixture with a second portion of the first medicament to form a dry powder inhalation composition, wherein the ratio by weight of the 2nd medicament/carrier ratio is less than the ratio by weight of the 1st medicament to the carrier, wherein the particulate carrier has a VMD of from about 50 to about 250 microns and (2) a dry powder inhalation composition made utilizing a method similar to (1), wherein the composition consists of (a) said particulate carrier, (b) said 1st particulate inhalant medicament, and (c) said 2nd particulate medicament.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Keller and Trofast were set forth on pages 4-5 and 5-7 of the office action mailed on November 13, 2006. In brief, Trofast teaches a particulate dry powder formulation comprising (a) formoterol fumarate dihydrate, (b) budesonide, and (c) lactose carrier particles, as well as methods of making said powder. Keller teaches dry powder compositions comprising (a) glycopyrrolate, (b) formoterol fumarate dihydrate, magnesium stearate, and lactose monohydrate carrier, wherein the powder can be made by mixing the ingredients with one another in any desired sequence.

Ward teaches a method for oral and pulmonary delivery of pharmaceuticals, wherein a powder formulation for use in a dry powder inhaler (DPI) comprises a pharmaceutical, which acts as its own carrier and is present as (a) microfine particles having a diameter in the range of 1-10 microns and **larger carrier particles** that have an **average volume median diameter** of 10-2,000 microns, preferably 30-300 microns, and **most preferably from 50-100 microns in**

diameter, and administration of the composition results in both a rapid onset pharmaceutical effect and a slower onset pharmaceutical effect (title; abstract; col. 2, lines 20-25 and 51-56; and claims 1-23). Ward teaches that suitable medicaments for use in the invented formulations include **beta-agonists** (i.e. a known class of bronchodilators), such as **albuterol**, **anti-inflammatories**, and **drugs for treating COPD** and other diseases (col. 4, lines 21-28). Ward teaches that the invented composition is desirable to improve patient compliance for patients taking more than one pharmaceutical (col. 1, line 60 through col. 2, line 13) and that, in general, inert carrier particles such as lactose upon inhalation administration are caught in the mouth and throat, swallowed, and exert no pharmaceutical effect (col. 3, lines 5-12).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Trofast lacks an explicit teaching about the order of steps used in preparing the dry powders. This deficiency is cured by the teachings of Keller. Trofast lacks the teaching of carrier particles having a volume median diameter ranging from about 50 to about 250 microns. This deficiency is cured by the teachings of Ward.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the invention to combine the teachings of Trofast, Keller, and Ward, because all references teach dry powder formulations for inhalation administration. Per the teachings of Keller, it would have been prima facie obvious to a person of ordinary skill in the art at the time of the instant

invention that one could adjust the order of mixing used to obtain an inhalable dry powder formulation. An ordinary skilled artisan cognizant of Ward 's teachings would have readily recognized that carrier particles having a volume median diameter ranging from about 50 microns to about 250 microns would be swallowed upon inhalation administration. An ordinary skilled artisan in the field of pharmaceutical formulations at the time of the instant invention (e.g. a pharmaceutical formulation scientist) would be capable of formulating an inhalable composition characterized by having a pharmaceutical effect exhibiting rapid onset properties through the use of an inert carrier, such as lactose, having a VMD ranging from 10-2,000 microns, more preferably 30-300 microns, and most preferably 50-100 microns. An ordinary skilled artisan would have had a reasonable expectation of success in modifying Trofast's invented formulations to utilize lactose carrier having an VMD ranging from 30-300 microns, because lactose is a well-known carrier used in inhalation formulations, such as the formulation taught by Trofast, and it is known in the art that inert carriers, like lactose, having a VMD from 30-300 microns are not inhaled and exert no pharmaceutical effect upon administration. Regarding the order in which the different components are combined, Keller teaches that the different ingredients can be mixed in any desired sequence. This teaching encompasses the following sequence of steps: blending a portion of 1st active particles with carrier particles to obtain a 1st mixture; combination of a 2nd active with the 1st mixture to obtain a second mixture; and finally admixture of the remaining 1st active particles to obtain a dry powder formulation. Mixing particulate components to obtain a dry powder composition is known as demonstrated by the cited prior art references.

Regarding claim 4, the amounts of active taught by Keller and Trofast would be sufficient to form a monolayer of each of these onto the carrier particles, the amount of actives taught by both Keller and Trofast meet are sufficient to create a monolayer of active onto the carrier surface as discussed on page 10 of the office action mailed on November 13, 2006. Therefore, an ordinary skilled artisan would have had reasonable expectation that mixing of the actives in the amounts taught by both references would obviously result in a coating of at least a monolayer onto the carrier particles. Regarding the "consisting of" langauge of claim 11 and claims dependent therefrom, Trofast teaches compositions consisting solely of (a) a 1st particulate medicament, (b) a 2nd particulate medicament, and (c) a particulate carrier; Keller is relied upon solely for the teaching of the order of mixing the particulate carriers; Ward is solely relied upon for the teaching of the desirable VMD of particulate carriers used in inhalable powder formulations.

Applicant has presented data in the instant specification (Tables 1-4) demonstrating the homogeneity of dry powders produced using Applicant's claimed method. This data is not convincing regarding the patentability of the claimed method, because it lacks a comparison of Applicant's method with the methods of the prior art. Applicant's claims 1-9 are open to a broad range of first and second medicament amounts and proportions. Even if Applicant's data in Tables 1-4 were somehow indicative of structural modification, this ground of rejection would still be proper because applicant's data was demonstrated with only 100:6 and 200:6 proportions of budesonide and formoterol fumarate dihydrate, wherein the total medicament concentration was in the range of about 5 wt%. In other words, Applicant's data is not commensurate in scope with what is being claimed in the cited claims, because these claims recite broad ranges and

claim 10 is not limited to a specific 1st and 2nd medicament mixed with carrier. Claims 1-6, 8, 10, and 16-19 are readable on (i) structurally different medicaments, (ii) much higher or lower total concentrations of medicaments, and (iii) much lower or higher weight ratios of first medicament to second medicament, e.g. 100,000,000:1 or 1:0.99,999. The term "bronchodilator" may refer to a broad range of structurally different compounds (e.g. betamimetics and anticholinergics), which although exhibiting bronchodilating effects have different mechanisms of action and secondary biological activities. The term anti-inflammatory steroid" is also broad and can refer to a great variety of compounds having a steroidal core, but differing in the degree, and sometimes the kind of biological activity exhibited, in addition to anti-inflammatory effects. Similarly, claims 7 and 9 are readable on compositions with (i) structurally different 2nd medicaments (claim 7) or 1st medicaments (claim 9), (ii) much higher or lower total concentrations of medicaments, and (iii) much lower or higher weight ratios of 1st medicament to 2nd medicament. Trofast's disclosed method of mixing the composition constituents would necessarily produce a dry powder that cannot be distinguished from the dry powder encompassed by applicant's broad claim language. These data do not demonstrate that the prior art methods do not yield dry powder formulations exhibiting the same or substantially similar physical properties/characteristics. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

The rejection of claims 1, 5-8, and 11-14 under 35 U.S.C. 103(a) as being unpatentable over Walz et al. (US RE 38,912) in view of Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent) **is withdrawn** per Applicant's claim amendments requiring that the claimed powder comprise carrier particulates with a VMD of from about 50 to about 250 microns.

Response to Arguments

Applicant's arguments with respect to claims 1-19 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Claims 1-19 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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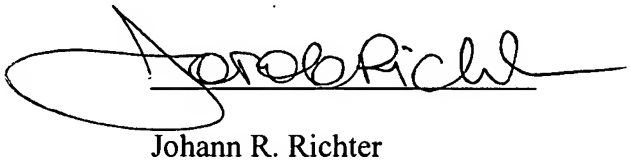

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